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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,449	04/04/2007	Yow-Pin Lim	61959US(51580)	2106

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,449	LIM ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *88,96,98 and 99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,12-15,21,25,27,28,31,40-42,45-48,56,57,77-86 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,10,12-15,21,25,27,28,31,40-42,45-48,56,57,77-86,88,96,98,99 and 101.

DETAILED ACTION

ACKNOWLEDGMENT TO PRIORITY, PRELIMINARY AMENDMENT, IDS, RESPONSE TO RESTRICTION REQUIREMENT, STATUS OF THE APPLICATION AND CLAIMS

1. This application is filed under 35 U.S.C. 371 on 04/04/07 having a filing date of 11/05/04 of PCT/US04/368481. Acknowledgement is made of Applicant's claim for priority based on U.S. Provisional Applications Serial Nos. 60/518,366 and 60/617,166 having a filing date of 11/08/03 and 11/08/04, respectively. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file. The preliminary amendment filed and the information disclosure statement (IDS) and Form PTO-1449 filed 05/04/06 and the response for restriction requirement filed 08/19/09, respectively are acknowledged, entered and considered. In view of Applicant's request claims 2, 10, 12-15, 21, 25, 27, 28, 31, 47, 48, 56, 57, 77, 78, 80, 81, 89, 98 and 101 have been amended and claims 3-9, 11, 16-20, 22-24, 26, 29, 30, 32-39, 43, 44, 49-55, 58-76, 87, 89-95, 97 and 100 have been canceled. Claims 2, 10, 12-15, 21, 25, 27, 28, 31, 47, 48, 56, 57, 77, 78, 80, 81, 88, 98 and 101 are active and pending in the application.

ELECTION WITH TRAVERSE

2. Applicant's election with traverse of Group I (claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86 and 101) in the communication filed 08/19/09 is acknowledged. The traversal is on the ground(s) that the subject matter of groups I-V

represents different embodiments of a single inventive concept for which a single patent should issue. The pending claims represent an intricate web of knowledge, continuity of effort, and consequences of a single invention, which merit examination of all these claims in a single application. Therefore, a search of all five groups in one search would not cause a serious burden to the Examiner (M.P.E.P §103).

Further, Applicant contends that even if the above-enumerated groups of claims are drawn to distinct inventions, the Examiner must still examine the entire application on the merits because doing so will not result in a serious burden. This is true given that: the five groups of claims are all directed to methods of using a blood plasma-derived Iαlp composition; the robust and extensive computerized search engines and databases at the Examiner's disposal; and the fact that in searching the use of a blood plasma-derived Iαlp, the Examiner will necessarily have searched all the various aspects recited in the pending claims. Therefore, searching all five groups of the invention, as defined in the Office action, would not cause a serious burden on the Examiner. Accordingly, the rejoining of Group I with Groups II-V of the inventions as presently divided by the Examiner would not be unduly burdensome to perform a search on all of the claims together of Groups I-V in the present application is noted.

However, Applicant's contention is not found persuasive for the reasons of record because the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The methods of Groups I-IV each has different scope, they are directed to various methods of using the

compositions (i.e., inter-alpha inhibitor proteins from human plasma) for different purposes. Although, Inventions I-IV are related, the end results of the aforementioned treatment and use of kit or prediction or monitoring are divergent and a search conducted for one would not necessarily overlap with a search conducted for another. Further, Inventions I-IV each differ from the other in a method of treating an inflammation related disorder, cancer and infectious disease in a subject and a kit formulation thereof (Group I), a method of treating a subject for acute inflammatory disease (Group II), a method for predicting a response to an I-alpha-Ip therapy (Group III), a method for monitoring the progress of a subject being treated with an I-alpha-Ip therapy (Group IV). Thus, the various methods using the same compositions/formulations as recited above do not correspond to the same technical feature and are not connected in design, operation or effect because they differ in method steps, parameters and reagents used, and as such, the methods as grouped are different from each other because they represent different technical features and different endeavors. Thus, the method of treating and use of a kit differs from the method for predicting or the method for monitoring and *vice versa* because the methods do not correspond to the same technical features and are not connected in design, operation or effect. Therefore, Groups I-IV does not share the same special technical features, the inventions do not relate to a single inventive concept.

With respect to Super Group V, the group has 8! = 40,320 possible kits, and as such, there is no unity of invention between all the possible kits. If Applicant elects Super Group V, then, Applicant has to choose or pick or elect **only one kit** among the

possibility of 40,320 kits. **This is NOT a species election but a restriction election within the Super Group.**

Therefore, Groups II-V (claims 88, 96, 98 and 99, respectively) are withdrawn as non-elected invention for the reasons of record. Hence, the Office action is directed to the merits of claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86 and 101(Group I) as *per* elected invention and Applicant is advised to cancel non-elected inventions of claims 88, 96, 98 and 99 (i.e., Groups II-V, respectively) in the next communication.

The requirement is still deemed proper and is therefore made FINAL.

OBJECTION OF THE CLAIMS

3. Claim 28 is objected in the recitation the acronym "DEAE". Use of full terminology at least in the first occurrence of the claim would obviate this objection. Also, claim 101 is objected in depending upon cancelled claims 54, 63 and 70, as well as depending and encompassing all the possible kit formulations as recited in claim 47, which is representative of Super Group V of non-elected invention of claim 99. Amendment of claim 101 to depend on claims 40 and 77 is suggested.

CLAIMS REJECTION-35 U.S.C § 103(a)

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffer et al (Journal of Chromatography B, Vol. 669, pp. 187-196, 1995) in view of Lim et al (The Journal of Infectious Diseases, Vol. 188, pp. 919-926, 15 September 2003) and Yang et al (Crit. Care. Med., Vol. 30, No. 3, pp. 617-622, 2002). Cited by Applicant on IDS filed 05/04/06.

The prior art of Hoffer et al generally describes the investigation of separation techniques in plasma fractionation and the removal of viruses through chromatographic means. The reference describes the method of obtaining the side fraction, which is a mixture of inter-alpha inhibitor protein and pre-alpha inhibitor protein during the purification of factor IX (FIX) from human blood plasma. The prior art states that FIX is routinely produced from human cryopoor plasma, wherein the

initial step is a solid-phase extraction of the cryopoor plasma with DEAE-Sephadex A50 followed by further chromatographic purification on DEAE-Sepharose FF. At this stage the product is subjected to the solvent/detergent (S/D) treatment with 1% Tween 80 and 0.3% tri-n-butylphosphate for 6 hours at 30^0 C. The S/D reagents are then removed, and separation of FIX, mainly from FX, is performed by means of affinity chromatography on Heparin-Sepharose CL 6B. The elute of the affinity column undergoes virus filtration. After this, the appropriate concentration is adjusted by means of ultra/diafiltration. A sterile filtration follows, and after lyophilization the final product is obtained. Further, SDS-PAGE was performed in order to monitor the additional purification that occurs during filtration process. Supports and buffers for chromatographic separation were used for anion-exchange chromatography, both on an analytical and preparative scale. Affinity chromatography was carried out with an analytical or preparative Heparin-Sepharose support. Analytical size-exclusion HPLC was performed on a tandem consisting various type of column and the other chromatographic conditions are listed in the legends of Figures 1-5. Thus, the reference clearly teaches the isolation and purification of human blood plasma product and composition thereof by means of various chromatographic techniques which resulted in increasing the specific activity of the product, and as such meets the limitations of claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42 and 78-80.

The primary reference of Hoffer et al differs from claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86 and 101 in not teaching a) a purified plasma fraction of inter-alpha inhibitory protein composition with a purity of inter-alpha

inhibitory protein ranging from 85% to about 100% pure; b) wherein the inter-alpha protein composition has a half-life of greater than 1 hour or 5 hours; having a molecular weight between about 60 to about 280 kDa; and a composition comprising H1, H2, H3 and H4; c) a kit formulation with a container thereof; and d) a method of treating human diseases such as an inflammation related disorders cancers, and infectious disease. Although, the primary reference as discussed above teaches the purification of the same product using substantially the same method; the product is expected to have substantially the same range of purity, molecular weights and composition comprising the heavy chains as well as the light chain because substantially the same product was purified by substantially the same methods. However, the secondary reference of Lim et al teaches the isolation and purification of human plasma-derived inter-alpha inhibitory protein by various chromatographic techniques wherein the purity of inter-alpha inhibitory protein was estimated to greater than 70%. The reference states that in normal plasma, bikunin (light chain) is found mostly in a complex form as inter-alpha inhibitor, which has a molecular weight of 225 kDa, and pre-alpha inhibitor, which has a molecular weight of 120 kDa. In inter-alpha inhibitor protein, bikunin is linked to 2 heavy polypeptide chains, H1 and H2, whereas, in pre-alpha inhibitor protein, only a single heavy chain (H3) is linked to bikunin (light chain). Similarly, the secondary reference of Yang et al teaches the isolation and purification of inter-alpha-inhibitor and pre-alpha inhibitory proteins by product from human plasma by the procedure involving ion-exchange and size-exclusion chromatography, wherein the administration of human inter-alpha inhibitors maintains

hemodynamic stability and improves survival rate from 30% to 89% in septic animals. The reference states that inter-alpha inhibitor is an approximately 220 kDa serum protein consisting of three polypeptides. Two of these, the heavy chains 1 and 2 (H1 and H2) are 75-80 kDa and have similar amino acid sequences. The third polypeptide, bikunin, has a molecular weight of 25 kDa and contains a 7 kDa chondroin sulfate chain. Thus, the secondary references clearly show that the claimed molecular weight overlaps with disclosed molecular weights of the references and the comprises the same light and heavy chains as claimed. In view of this, it would have been obvious to one of ordinary skill in the art to combine the secondary references because the secondary references teach the use of specific molecular weights and heavy chains as claimed for treatment of human diseases such inflammations and infections. Thus, in view of the above, it would have been obvious to one of ordinary skill in the art to combine the secondary references teachings (i.e., use of molecular weights and heavy chains) for the same purposes into the primary reference's teachings because such features are known and suggested in the art as seen in the secondary references, and including such features into the composition and methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

In regard to claim 77, the claim is directed to a product by process claim comprising a composition of inter-alpha inhibitory protein produced by the process of claim 1. The novelty and patentability of the claimed product (i.e., a composition of inter-alpha inhibitory protein) is based on the claimed components of the product and

not on the recited process step(s), and as such the prior art product renders the claim obvious. With respect to claim 101, the claim is directed to a kit formulation comprising a container including inter-alpha inhibitory protein and a label or package insert with instruction for therapeutic use thereof. The combined teachings of the references teaches the composition and/or formulation that would have been found in the claimed composition and/or kit to formulate composition into a kit format because the claimed kit is tailored for use in the claimed kit formulation comprising the composition claimed. Hence, it would have been expected to package the composition and instructions thereof required for the method into kit format of the well-known commercial expediency of doing so.

Therefore, in view of the above and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to employ a kit for Ialp therapy comprising a composition as claimed in claims 40 or 77 with instructions for therapeutic use thereof. Accordingly, the combined teachings of the prior art clearly discloses a process for purification or producing a blood plasma-derived inter-alpha inhibitory protein and pre-alpha inhibitory protein, pharmaceutical and kit formulation thereof and to a method of treating an inflammation related disorder, cancer and infectious diseases in a subject, and as such, substantially discloses the invention and renders claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 4-42, 45-48, 56, 57, 77-86 and 101 *prima facie* obvious, absent of sufficient objective factual evidence or unexpected results to the contrary.

CONCLUSAION AND FUTURE CORRESPONDANCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654